Commentary: Non-inferiority trial: the devil is…

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Central message: non-inferiority trials need thorough understanding of statistical and technical peculiarities as to have a valuable clinical impact.

Central picture: Arnaldo Dimagli, MD (left) and Umberto Benedetto MD, PhD (right)

There are three main types of clinical trials based on the statistical hypothesis tested. “Superiority” trials compare two treatments to determine which is better; “equivalence” trials test whether a new treatment is as effective as the standard treatment; “non-inferiority” trials have the aim to demonstrate that a new experimental treatment is not unacceptably worse than the standard treatment. These latter studies are being more and more embraced [1] because they allow to study new treatments which can bring an advantage in terms of costs, patient’s compliance to medication, fewer adverse effects or greater availability [2].

In this issue, Falk and Friede focus on the main aspects of non-inferiority trials with prodigious attention to details [3]. The authors describe the critical step of choosing a non-inferiority margin, that is the value which the effect measure of the experimental treatment must not exceed when compared to the standard treatment to prove its non-inferiority. The non-inferiority margin should be oriented from both a statistical and a clinical point of view and should be prospectively calculated and clearly reported in the protocol of the study [4]. Once the non-inferiority margin is set, the trial null hypothesis will test that the treatment difference between the standard and the experimental strategy is equal or greater than the assumed margin while the alternative hypothesis will state that the efficacy value of the standard treatment and the experimental treatment differ by no more than the margin. It is important to acknowledge the different statistical hypothesis which are being tested in superiority and inferiority trials in order to interpret results accordingly. In a superiority trial the acceptance of the null hypothesis, that tests if the new treatment is not superior to the standard one, does not allow us to draw a conclusion of non-inferiority because this would lead to a biased estimate. Conversely, in a non-inferiority trial when the null hypothesis is rejected, we assume that the new treatment is non-inferior to the comparator and that the two treatments only differ by clinically irrelevant effects.

But what does clinically irrelevant mean for our patients? A practical example may help. Would you accept to buy a house located in a less safe neighborhood just because it is less expensive than another

one in a safer area? If the difference in the crime rate were only of 0.1%, it would be reasonable to save 10% on the cost of the house, but if the saving were 0.1% and the crimes rate were 10% higher it would be hard to fairly choose the cheapest house. This applies to our patients in our daily practice. As suggested by the European Medicines Agency [4], there are areas where mortality or other irreversible morbidities (e.g. stroke) may not allow any margin of inferiority. It would be of extreme difficulty to ethically accept the excess rate in deaths to compare a new treatment just because it is less expensive or with minor adverse effects. For example, a *quater in die* drug A has proved over decades to be safe and efficient in preventing death, stroke and myocardial infarction. A new *quaque die* treatment B would be positively accepted for its anticipated better compliance to treatment as long as it will not cause more deaths, strokes and myocardial infarctions than drug A. Here comes an intriguing paradox: if we assume that drug B will increase the compliance to the treatment, we can reasonably anticipate that there will be a relevant advantage which translates into a superior outcome and goes beyond the pure evidence of having only a more comfortable regimen for the patient. So non-inferiority is being tested when superiority could be proved.

Concluding, non-inferiority trials can represent a rigorous method to widen treatment options in proper settings, but physicians should carefully read and understand the deepest statistical and technical pieces of them in order to verify that a proper non-inferiority margin was chosen and assess the extent of the clinically irrelevant events.

References

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